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Gene Section
Review

CCNB1 (cyclin B1)

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Identity

Other names: CCNB

HGNC (Hugo): CCNB1

Location: 5q13.2

DNA/RNA

Description

9 exons; 2,087 bp; 433 residues CCNB1 transcript 1.
8 exons; 1,833 bp; 397 residues CCNB1 transcript 2.

Transcription

Two alternative transcripts resulting from distinct transcription initiation sites. One is constitutively expressed and the other is G2/M cell cycle-regulated.

Pseudogene

No verified pseudogenes.

Protein

Description

Cyclin B1 (48.337 kDa) is a member of the cyclin family of proteins whose levels vary during the cell cycle in order to activate specific cyclin-dependent kinases (CDKs) required for the proper progression through the cell cycle. Cyclin B1 protein begins to increase during G2, peaks in mitosis, and is rapidly degraded before the cell cycle is completed. Cyclin B1 interacts with CDK1 to form a complex known as the maturation-promoting factor (MPF), which is essential for cell cycle progression through mitosis. When chromosomes are properly aligned during anaphase, rapid degradation of cyclin B1 by anaphase-promoting complex/cyclosome (APC/C) is required for mitotic exit and completion of the cell cycle.

Expression

Cyclin B1 is overexpressed in a variety of cancers compared to normal cells and tissues. In normal tissues, low levels of cyclin B1 is detected in testis, thymus, bone marrow, and smooth muscle (CCNB1 expression). In most primary tumors, the expression of cyclin B1 is "unscheduled" (unrestricted to particular phases of the cycle), whereas in normal lymphocytes, the expression of cyclin B1 is restricted to very late S and G2 + M phases of the cell cycle (Gorczyca et al., 1997).

Localisation

During interphase, cyclin B1 is concentrated in the cytoplasm but can shuttle to the nucleus (Pines and Hunter, 1991).

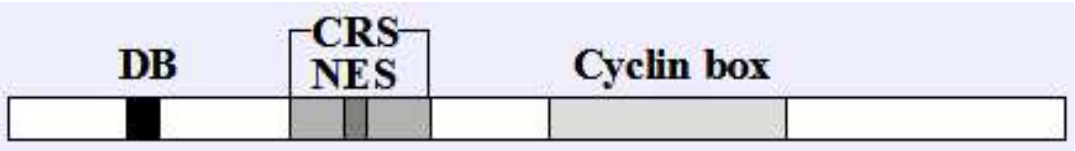

Diagram of sequence domains for cyclin B1. The destruction box (DB) is required for degradation of cyclin B1 at the metaphase-to-anaphase transition. The cytoplasmic retention sequence (CRS) and the nuclear export signal (NES) are critical determinants of cyclin B1 localization during mitosis. The cyclin box is required for interaction with CDK1.

At prophase, cyclin B1 accumulates in the nucleus and then to condensed chromatin, spindle microtubules, centrosomes, and chromatin during prometaphase (Bentley et al., 2007; Chen et al., 2008). This corresponds to localization of known CDK1 substrates, including nuclear lamins, microtubule and chromatin-associated proteins. Cyclin B1 is preferentially localized to unattached kinetochores and is involved in chromosome alignment in mitosis. In carcinomas, cytoplasmic expression of cyclin B1 is associated with a specific T-cell immune response (Egloff et al., 2006).

Function

At entry into mitosis, cyclin B1-CDK1 promotes chromosome condensation, nuclear lamina resolution, and mitotic spindle assembly. Knockout mice without cyclin B1 or CDK1 are embryonic lethal, suggesting a requirement for cell proliferation (Brandeis et al., 1998). A long list of potential substrates for cyclin B1-CDK1 suggests other functions not yet known (CDK1 substrates).

Homology

Cyclin B1 is a member of the highly conserved cyclin family and cyclin AB subfamily. The cyclin box is a region of protein sequence homology that is common to all members of the cyclin family and is required for interaction with CDK partner. There are at least three G1 cyclins (cyclin C, cyclin D, cyclin E) and two G2/M cyclins (cyclin A, cyclin B). Cyclin B2 also interacts with CDK1 but is not required for cell proliferation (Brandeis et al., 1998). Cyclin B3 binds to CDK2 and appears to function in meiosis (Nguyen et al., 2002).

Mutations

Note

There are no known germinal or somatic mutations for cyclin B1 (CCNB1 COSMIC).

Implicated in

Prostate carcinoma

Disease

One study shows that the most powerful predictor of time to relapse of prostate cancer is a high ratio of cyclin A and B to the proliferation marker Ki67, i.e., the higher the ratio the longer time to relapse (Marshal et al., 1996). Another study, however, shows that high cyclin B1 expression in prostate cancer correlates with tumor grade and DNA ploidy but does not correlate with disease recurrence (Kallakury et al., 1999). Lower level of endogenous cyclin B1 increases the sensitivity of DNA mismatch repair-deficient prostate cancer cells to alkylating agents (Rasmussen et al., 2000). Overexpression of the oncogenic serine/threonine kinase PIM1 in prostate cancer cells increases cyclin B1 protein expression, which contributes to the development of polyploidy by delaying cytokinesis (Roh et al., 2005). The levels of cyclin B1 protein correlate with the ability of chemotherapy drugs to induce apoptosis of prostate cancer cells in vitro (Gomez et al., 2007).

Breast carcinoma

Disease

Treatment of MCF7 breast cancer cells with cyclin B1-specific antisense oligonucleotide blocks Taxol-induced apoptosis, suggesting that cyclin B1-associated CDK1 activity plays an important role in the induction of apoptosis by Taxol (Shen et al., 1998). Memory T cells specific for cyclin B1 peptides were isolated from patients with breast cancer (Kao et al., 2001). Nuclear cyclin B1-positive breast carcinoma is resistant to adjuvant therapy, and nuclear cyclin B1 immunoreactivity is a potent prognostic factor in breast carcinoma patients (Suzuki et al., 2007). However, another study did not find a correlation with cyclin B1 overexpression and a worse outcome in breast cancer patients (Peters et al., 2004). Downregulation of cyclin B1 inhibits proliferation of breast cancer cell lines and sensitizes to Taxol (Yuan et al., 2004; Androic et al., 2008).

Non-small cell lung carcinoma (NSCLC)

Disease

Cyclin B1 is deregulated in NSCLC, particularly in the squamous cell carcinoma subtype (SCC), and a high level of cyclin B1 expression may be a prognostic marker for patients with early-stage SCC of the lung (Soria et al., 2000). Elevated levels of cyclin B1 expression may be an indicator of poor prognosis in NSCLC, particularly in non-SCC (Arinaga et al., 2003; Yoshida et al., 2004; Singhal et al., 2005). One study, however, did not find a prognostic relevance for cyclin B1 in NSCLC (Yoo et al., 2007).

Small cell lung carcinoma

Disease

Cyclin B1 expression closely correlates with the Ki-67 labeling index in small cell lung carcinomas, suggesting that cyclin B1 is one of the key factors regulating cell proliferation in pulmonary neuroendocrine tumors. However, cyclin B1 did not correlate with patient survival (Igarashi et al., 2004).

Esophageal squamous cell carcinoma (ESCC)

Disease

Cyclin B1 expression, especially nuclear, can be significant as a prognostic indicator in ESCC and may indicate a poor prognosis for patients (Murakami et al., 1999; Nozoe et al., 2002; Takeno et al., 2002). Isogenic ESCC cells overexpressing cyclin B1 reveal strong invasive growth and high potential of metastasis to lung in xenograft mice (Song et al., 2008).

Head and neck squamous carcinoma (HNSCC)

Disease

HNSCC overexpressing cyclin B1 may be resistant to radiation therapy and cyclin B1 may be an indicator of the risk of recurrence and metastasis in patients having HNSCC receiving radiation therapy (Hassan et al., 2002).

Renal cell carcinoma (RCC)

Disease

Increased cyclin B1 in RCC and aberrant localization within the cytoplasm of tumor cells positively correlates with tumor progression, indicating the significant role of cyclin B1 in the development and pathogenesis of RCC. There may be prognostic value of cyclin B1 for RCC patients (Ikuerowo et al., 2006).

Cervical carcinoma

Disease

The relationship between human papillomavirus virus (HPV) typing and cyclin B1 expression was not significant in cervical intraepithelial neoplasia and invasive cancer (Hashiguchi et al., 2004). HPV-16 E1 E4 protein sequesters CDK1/cyclin B1 onto the cytokeratin network, prevents the accumulation of active CDK1/cyclin B1 complexes in the nucleus, and hence prevents mitosis. This may create an environment optimal for viral DNA replication (Davy et al., 2005). HPV-18 decreases the fidelity of mitotic checkpoints and increases CDK1-associated kinase activity relative to control populations. The G2 checkpoint is aberrant by virtue of the stabilization of cyclin B1 mRNA through the upregulation of HuR protein (Cho et al., 2006). Up-regulation of cyclin B1 expression occurs in cervical cancer and an aberrant expression of cyclin B1 might play an important role in cervical carcinogenesis (Zhao et al., 2006). Reduction of cyclin B1 in HeLa cervical carcinoma cell lines inhibits proliferation, induces apoptosis, and sensitizes to Taxol (Yuan et al., 2006).

Ovarian carcinoma

Disease

There is a significant correlation between percentages of polo-like kinase (PLK)-positive cells and histological grade of ovarian cancer. However, the expression of proliferating cell nuclear antigen, Ki-67, and cyclin B1 is independent of PLK expression (Takai et al., 2001).

Pancreatic cancer

Disease

Overexpression of CDK1, cyclin A, and cyclin B1 occurs in 54.8, 54.9 and 56.4%, respectively, of the pancreatic adenocarcinomas. The findings suggest that CDK1 and cyclin A play a role in the progression of pancreatic adenocarcinoma, while the clinical significance of cyclin B1 remains to be clarified because of its more random expression (Ito et al., 2002).

Liver cancer

Disease

Fifteen of 100 patients with hepatocellular carcinoma (HCC) have autoantibodies reactive with cyclin B1 (Covini et al., 1997). CDK1 overexpression is directly related to advanced stage, portal invasion, intrahepatic metastasis, poor differentiation, high alpha-fetoprotein level, large size, high Ki-67 labeling index, and poor prognosis. Cyclin A and B1 overexpression shows a similar tendency to that of CDK1, but they are not recognized as independent prognostic factors (Ito et al., 2000). Hepatitis C virus (HCV) proteins increase the activity of the cyclin B1-CDK1 complex via the p38 MAPK and JNK pathways and promotes nuclear import of cyclin B1 (Spaziani et al., 2006). TIS21 negatively regulates hepatocarcinogenesis in part by disruption of the FoxM1-cyclin B1 regulatory loop, thereby inhibiting proliferation of transformed cells developed in mouse and human livers (Park et al., 2008).

Gastric cancer

Disease

Cyclin B1 overexpression does not correlate with survival of patients with gastric cancer (Brien et al., 1998). Another study shows that cyclin B1 protein overexpression is closely associated with less aggressive gastric cancers (Yasuda et al., 2002). A third study shows that overexpression of cyclin B1 may play an important role in lymph node metastatic potential of gastric cancer (Kim, 2007).

Colorectal adenocarcinoma

Disease

The majority of colorectal cancers express high levels of cyclin B1, consistent with a high rate of cell proliferation (Wang et al., 1997). Cyclin B1 expression does not change in recurrent colorectal adenocarcinoma compared to primary tumors (Seong et al., 1999). A study suggests a close correlation between a lack of cyclin B1 immunostaining and a stronger metastatic behavior in colorectal cancer (Korenaga et al., 2002). Cyclin B1, but not cyclin G1, may promote colorectal carcinogenesis and later metastasis to lymph nodes (Li et al., 2003). High expression of cyclin B1 is a frequent and early event in colorectal carcinomas. However, cyclin B1 expression is neither a predictor of prognosis or survival in patients with colorectal cancer nor a suitable tool for identifying subgroups of patients at higher risk for disease recurrence (Grabsch et al., 2004; Bondi et al., 2005). Adenomatous polyposis coli (APC) is a substrate for recombinant human CDK1-cyclin B1, implicating phosphorylation as a mechanism for regulating APC function via a link to the cell cycle (Trzepacz et al., 1997).

Thyroid carcinoma

Disease

Cyclin B1 is overexpressed in four undifferentiated thyroid carcinomas (19.0%), but not in thyroid carcinomas of other types. CDK1 overexpression is also related to carcinoma differentiation ($p < 0.0001$), and is directly linked to cyclin A overexpression ($p < 0.0001$), but not to cyclin B1 overexpression (Ito et al., 2002). Cyclin B1 expression does not have any prognostic significance for poorly differentiated follicular thyroid carcinoma (Pulcrano et al., 2007).

Tongue carcinoma

Disease

Cyclin B1 is overexpressed in a subset of squamous cell carcinoma of the tongue and is associated with a more aggressive biological behavior of the disease (Hassan et al., 2001).

Skin melanoma

Disease

The expression of cyclin B1 ($P < 0.0001$) is significantly higher in melanomas in comparison with Spitz nevi (Stefanaki et al., 2007).

Glioma

Disease

Cyclin B1 is a gene identified to be increased in glioma cells invading brain slice cultures (Holtkamp et al., 2005). Human glioma tissue microarrays indicate a positive expression rate of CDK1/cyclin B1 with a positive correlation with pathologic grades (Chen et al., 2008).

Astrocytoma

Disease

Nuclear and cytoplasmic cyclin B1 immunostaining correlates well with the tumor grade but shows poor correlation with Ki-67 in astrocytomas (Allan et al., 2000). There is a significant increase in cyclin B1 ($P = 0.002$) expression with increasing grade from diffuse astrocytoma through anaplastic astrocytoma to glioblastoma, suggesting a potential as a marker of tumor grade (Scott et al., 2005).

Medulloblastoma

Disease

Cyclin B1 expression shows no statistical significant effect on survival in medulloblastoma (Neben et al., 2004). Another study shows that the combined expression of MYC and the lactate dehydrogenase B (LDHB)/cyclin B1 gene signature is able to predict survival in medulloblastoma patients and are strong prognostic markers independent of the clinical parameters, metastasis, and residual disease (de Haas et al., 2008).

Osteosarcoma

Disease

E2F-1 overexpression in the U2OS osteosarcoma cell line increases cyclin B1, CDK1 activity, sensitivity to paclitaxel, and the cellular growth rate. Knockdown of cyclin B1 using an RNA interference decreases cellular growth rate and an increases resistance to paclitaxel (Russo et al., 2006).

Leukemia and lymphoma

Disease

Derangement of cyclin B1 and CDK1 kinetics and functions is more profound in Hodgkin's disease than in anaplastic large cell lymphomas (Leoncini et al., 1998). Cyclin B1 and CDK1 appears to be involved in the genesis or progression of malignant lymphoma but only CDK1 is a useful marker for response to chemotherapy (Jin and Park, 2002). Overexpression of cyclin B1 in follicular lymphomas correlates with better response to chemotherapy (Bjorck et al., 2005). Nuclear and/or cytoplasmic staining in > or = 1% of diffuse large B-cell lymphoma cells is significantly associated with shorter overall survival (Obermann et al., 2005). Cyclin B1 protein accumulates in the nucleus of cells that are sensitive to gamma radiation-induced apoptosis (thymocytes, lymphoid cell lines), but remains cytoplasmic in apoptosis-resistant cells (primary and transformed fibroblasts) (Porter et al., 2003).

Alzheimer's disease (AD)

Disease

Cyclin B1 and CDK1 are enriched in neurons with neurofibrillary tangles (NFT), characteristic of AD. This suggests that aberrantly reexpressed cyclin B1/CDK1 in NFT-bearing neurons in AD brain contributes to the generation of M-phase phospho-epitopes in NFT (Vincent et al., 1997). Cyclin B1 is not detected in control subjects but is expressed in subiculum, dentate gyrus, and CA1 region of patients with AD pathology (Nagy et al., 1997). Aberrant expression of cyclin B1 is identified in the hippocampus, subiculum, locus coeruleus, and dorsal raphe nuclei, but not inferotemporal cortex or cerebellum of AD cases. Control subjects show no significant expression of cyclin B1 in any of the six regions. Disregulation of various components of the cell cycle may be a significant contributor to regionally specific neuronal death in AD (Busser et al., 1998). Direct interactions between cyclin B1 and Abeta may provide potential mechanisms for the cytotoxicity of the Abeta peptide (Milton, 2002). CIP-1-associated regulator of cyclin B (CARB), a protein that associates with cyclin B1, increases in intraneuronal NFT neurofibrillary tangles in susceptible hippocampal and cortical neurons in AD. By marked contrast, CARB is

found only at background levels in these neuronal populations in nondiseased age-matched controls (Zhu et al., 2004). Cdh1/Hct1, an activator of the E3-ubiquitin ligase anaphase-promoting complex (APC) that promotes the ubiquitylation and degradation of mitotic cyclins, is required to prevent the accumulation of cyclin B1 in terminally differentiated neurons. By keeping cyclin B1 low, Cdh1 prevents these neurons from entering an aberrant S phase that leads to apoptotic cell death.
These results provide an explanation for the mechanism of cyclin B1 reactivation that occurs in the brain of patients suffering from AD (Almeida et al., 2005).

Neurodegenerative disease

Disease

Neurons containing characteristic neurodegenerative lesions in a subset of diseases including Down Syndrome, Frontotemporal Dementia linked to chromosome 17, Progressive Supranuclear Palsy, Corticobasal Degeneration, Parkinson-Amyotrophic Lateral Sclerosis of Guam, Niemann Pick disease type C, and Pick's disease also display mitotic indices including cyclin B1 expression (Husseman et al., 2000).

Cytogenetics

Chromosome instability resulting from Tax-induced deficiency of cyclin B1 and securin may be the explanation for the highly aneuploid nature of adult T-cell leukemia cells (Liu et al., 2003).

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